REMARKS

Upon entry of the foregoing amendment, claims 258-345 are pending in the application, with 258, 302, 334, and 340 being the independent claims. Claims 178-257 have been canceled without prejudice or disclaimer. New claims 258-345 have been added. Support for the new claims is found in the specification as described in the amendment filed February 8, 2007. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 112

Claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251, and 253-256 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, for the introduction of new matter. (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner alleges that the phrases "compressible blend" and "the only component of the dosage form that enhances absorption of the drug across said epithelial cell lining" and claims requiring all components of the dosage form to be solid at room temperature do not have adequate support in the specification. (Office Action, pages 2-3).

Applicants respectfully disagree. Claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251, and 253-256 have been canceled, rendering the rejection moot. New claims 258-337 do not contain these phrases.

Applicants respectfully request that the rejection of claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251, and 253-256 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251, and 253-256 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Watts *et al.* (International Application No. WO 97/05903) in view of Heiber *et al.* (U.S. Patent No. 5,346,701), and optionally any one or more of Teng *et al.* (U.S. Patent No. 6,747,014), Garces *et al.* (U.S. Patent No. 5,736,161), and Bachynsky *et al.* (U.S. Patent No. 5,190,748). (Office Action, page 4). Applicants respectfully traverse this rejection.

Claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251, and 253-256 have been canceled, rendering the rejection moot. Applicants respectfully request that the rejection be withdrawn. Insofar as the Examiner may choose to apply this rejection to the pending claims, the following comments are provided.

As stated in the recently published Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co*...." (Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some **suggestion or incentive that would have motivated** the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a **reasonable expectation of success**, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references **must teach or suggest all of the limitations of the claims**. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All

words in a claim must be considered in judging the patentability of that claim against the prior art").

The present claims are directed to pharmaceutical compositions and solid oral dosage forms comprising the pharmaceutical compositions, wherein the compositions consist of a hydrophobic or macromolecular drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. The transitional phrase "consisting of" indicates that there are no unlisted components present in the pharmaceutical compositions.

In contrast, Watts *et al.* discloses unambiguously the use of a ***two-component*** absorption promoter as follows.

> The present invention therefore provides a drug delivery composition for colonic delivery comprising a polar drug, an absorption promoter which (a) comprises a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof *and a dispersing agent* or (b) comprises a mixture of mono/diglycerides of medium chain fatty acids *and a dispersing agent* and means adapted to release the polar drug and absorption promoter in the colon.

Watt *et al.*, page 5, lines 10-16 (emphasis added). Both of the Watts *et al.* embodiments describe the absorption promoter as a two-component mixture in which one component ***must*** be a dispersing agent while the other may be either: (1) a medium chain fatty acid or salt; or (2) a mixture of mono/diglycerides of medium chain fatty acids. Clearly, the scope of the disclosure of Watts *et al.* extends ***only*** to the use of two-component absorption promoters. All of the embodiments which employ a medium chain fatty acid or salt thereof in the absorption promoter ***must also contain*** a dispersing agent as a second component of the absorption promoter. Watts *et al.* defines the term "dispersing agent" to include "an agent that is able to position itself at the interphase between the formulation phase and the aqueous phase in the colon and thereby reduce the interfacial tension between the two phases and promote the dispersion of the formulation in the lumen of the colon." Watts *et al.*, page 5, line 30 to page 6, line 4.

The presently claimed pharmaceutical compositions do not have a two-component absorption enhancer and do not contain any type of dispersing agent as defined in Watts *et al.* Thus, Watts *et al.* does not disclose compositions consisting of each of the components as recited in the present claims. Moreover, Watts *et al.* does not provide any suggestion or incentive to produce compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list.

As previously noted, Watts *et al.* discloses a composition of sodium insulin and capric acid in a comparative example (Example 3) in order to demonstrate the inferior effect of capric acid as the only enhancer compared to the synergistic effect realized by their two component absorption promoter. It is important to note that this disclosure is limited ***only*** to capric acid, and does not include any disclosure of any medium chain fatty acid salt, by itself, in combination with a drug. As demonstrated in the samples presented in the interview with the Examiner held on October 16, 2007, sodium caprate is a flowable, compressible, water-soluble powder at room temperature, whereas capric acid is a congealed, incompressible, and water-insoluble mass. As shown in the table below, there are very substantial differences in the physical properties of capric acid as compared with its sodium salt. These differences carry over into the resultant properties of mixtures of each with an active ingredient, and these differences are significant.

	Sodium caprate	Capric acid
Molecular Formula	$C_{10}H_{19}O_2Na$	$C_{10}H_{20}O_2$
Melting Point	240°C	31°C
Description	White to cream colored powder	White crystals
Solubility	Soluble in water	Immiscible in water

With regard to the teachings of Watts *et al.*, a composition of sodium insulin and capric acid, as described in Example 3 of Watts *et al.*, was produced in accordance with the

teachings of Watts *et al.* *See* Declaration of James Swarbrick, P.Sc., Ph.D. filed November 5, 2007 ("Swarbrick Declaration") at ¶ 15. As noted above, capric acid has a melting point of 31°C and is immiscible in water. Because its melting point is so close to room temperature, one of skill in the art would recognize that it is very difficult, if not impossible, to form a homogenous particulate mixture of capric acid with an active ingredient having a sufficiently small particle size to be suitable for tableting or dry encapsulation. The very act of mechanically mixing capric acid with an active ingredient will impart sufficient energy to the capric acid to cause it to melt. To avoid this, Watts *et al.* teaches one to melt capric acid by heat and to add the solid insulin to the resulting liquid. The final composition, at room temperature, is a semi-solid mass of capric acid and sodium insulin in the form of a paste. *Id.* In such form, it does not flow freely into a tablet press and is difficult to compact into a tablet. *Id.* at ¶ 8. Where such material can be compacted, it is difficult to form a tablet that is properly released from the tablet press and that has the requisite structural integrity. *Id.*

By contrast, sodium caprate has a very high melting point so that a homogenous particulate mixture of sodium caprate and an active ingredient that has sufficiently suitable characteristics for tableting or dry encapsulation may be readily formed. Due to its high solubility in water, tablets manufactured with a sodium caprate mixture will dissolve very quickly and will have a drug load that can be readily absorbed. As a result, the comparative example in Watts *et al.* of a mixture of capric acid and sodium insulin is a disclosure quite unlike, and indeed no way suggestive of, compositions and dosage forms comprising a drug and a medium chain fatty acid salt as the sole enhancer, as recited in the present claims.

Moreover, insofar as Watts *et al.* demonstrates the inferiority of the insulin/capric acid mixture of the comparative example as compared to mixtures utilizing a two-competent absorption enhancer, Watts *et al.* teaches away from using a medium chain fatty acid or salt as the sole enhancer. Moreover, Watts *et al.* states that:

> [b]oth fatty acids and polyglycolyzed glycerides are known individually to increase absorption of polar drugs from the colon. However, in order to achieve an acceptable effect in a large mammal such as a pig or man a large quantity of the material must be used. The quantity required is too great to be administered.

Watts *et al.*, page 13, lines 24-28. This is an express teaching away from the claimed invention. Further, all of the compositions of Watts *et al.* which include a medium chain fatty acid are disclosed in the form of a suspension in liquid form or cooled to a semi-solid. There is no teaching or suggestion to provide such compositions in any other form, and in particular, in a compressible form.

While one might nonetheless suggest from the teachings of Watts *et al.* that medium chain fatty acids and their corresponding salts are interchangeable insofar as either may be used, it is critical to bear in mind that such suggested "interchangeability" must be viewed ***within the context*** of the two-component microemulsions of Watts *et al.* When viewed outside of this context, such as in a context concerning compressible blends of a drug and an enhancer in particulate form, this interchangeability cannot be presumed to follow and is not provided by the teachings of Watts *et al.* From the physical data describing capric acid and sodium caprate summarized in the table above, it is evident that there is no basis to consider these materials to be interchangeable in the context of a compressible blend of a drug and an enhancer.

Heiber *et al.* does not remedy the deficiencies in Watts *et al.* Heiber *et al.* discloses compositions for administering a drug to the oral mucosa. The compositions comprise a macromolecular drug, a bile salt or bile salt analog, and a hydrophilic polymer. Heiber *et al.*, column 5, lines 14-24. Heiber *et al.* does not disclose any compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. Moreover, Heiber *et al.*, taken either alone or in view of Watts *et al.*, does not provide any suggestion or incentive to produce such a composition.

Teng *et al.* does not remedy the deficiencies in Watts *et al.* Teng *et al.* relates to pharmaceutical compositions for delivery of oligonucleotides. The compositions comprise various absorption enhancers selected from the classes of surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Teng *et al.*, column 7, lines 44-50. Teng *et al.* does not disclose any compositions consisting of a drug, one or more absorption

enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. Teng *et al.* taken either alone or in view of the other cited references, does not provide any suggestion or incentive to produce such a composition.

Garces *et al.* does not remedy the deficiencies in Watts *et al.* Garces *et al.* relates to pharmaceutical compositions comprising millispheres made up of drugs mixed with gellable hydrocolloids and coated with cationic polysaccharides. Garces *et al.*, column 2, lines 10-27. Garces *et al.* does not disclose any compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. Garces *et al.* taken either alone or in view of the other cited references, does not provide any suggestion or incentive to produce such a composition.

Bachynsky *et al.* does not remedy the deficiencies in Watts *et al.* Bachynsky *et al.* relates to pharmaceutical compositions comprising an antibacterial compound and a two-component absorption–enhancing system made up of (1) an ether of a C_6 to C_{18} alcohol and a polyoxyethylene glycol and a second component selected from among (2)(i) a polyoxyethylene glycol C_6 to C_{18} carboxylic acid glyceride ester, (2)(ii) a C_6 to C_{18} carboxylic acid or pharmaceutically acceptable salt thereof and (2)(iii) an ester of two or more C_6 to C_{18} carboxylic acids, glycerol and a polyoxyethylene glycol. Bachynsky *et al.*, column 2, lines 3-19. Bachynsky *et al.* does not disclose any compositions consisting of a drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. Bachynsky *et al.* taken either alone or in view of the other cited references, does not provide any suggestion or incentive to produce such a composition.

Thus, none of the cited references, either alone or together, teach all of the limitations of the present claims as none of the references disclose a pharmaceutical composition ***consisting of*** a hydrophobic or macromolecular drug, one or more absorption enhancers, each of which is a salt of a medium chain fatty acid having a carbon length of from 8 to 14 carbon atoms, and one or more excipients selected from a recited list. In addition, none of the cited

references provide any suggestion or incentive to modify the compositions disclosed therein to contain a medium chain fatty acid salt in particulate form as the only absorption enhancer, and none of the cited references provide a reasonable expectation that a composition containing a medium chain fatty acid salt in particulate form as the only absorption enhancer would successfully deliver a drug to the intestine.

CONCLUSION

Accordingly, Applicants submit that the present application is in condition for allowance and the same is earnestly solicited. Should the Examiner have any small matters outstanding of resolution, he is encouraged to telephone the undersigned at 919-854-1400 for expeditious handling.

Respectfully submitted,

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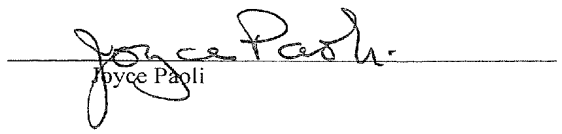
Signature: 
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